Pharmaceuticals and Personal Care Products (PPCPs) as Environmental Pollutants

◂ *Pollution from Personal Actions* ▸

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U.S. EPA Notice

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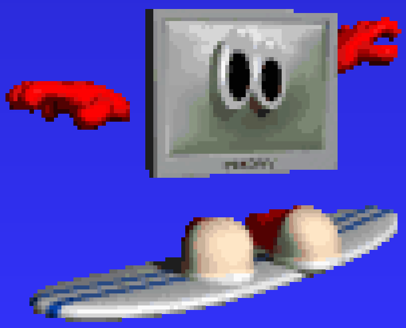
NOTE

Because of the size of this presentation, this file comprises only the 2nd part of the entire PPCPs slide presentation. The subsequent parts must be accessed separately.

These slides and many additional materials are available at the U.S. EPA's ***PPCPs Web Site***:

http://www.epa.gov/nerlesd1/chemistry/pharma/index.htm



“Emerging” Risks

Previously unidentified or under-appreciated aspects of chemical pollution often involve chemical classes not before recognized as pollutants — there is nothing rigorous or definitive about the established lists of pollutants.

However, any concern for ecological or human health risk posed by newly considered chemical classes must have a scientific basis in environmental **occurrence**, **exposure**, and ultimately a measurable **effect**.

One of the EPA’s 10 Strategic Plan goals — Goal 8 (*Sound Science*): Improved Understanding of Environmental Risk, and Greater Innovation to Address Environmental Problems [see: http://www.epa.gov/ocfopage/plan/plan.htm]

continued -

“Emerging” Risks

It is reasonable to surmise that the occurrence of PPCPs in waters is not a new phenomenon. It has only become more widely evident in the last decade because continually improving chemical analysis methodologies have lowered the limits of detection for a wide array of xenobiotics in environmental matrices. There is no reason to believe that PPCPs have not existed in the environment for as long as they have been used commercially.

continued -

"Emerging" Risks

While PPCPs as environmental pollutants are often referred to as an "emerging issue," the term "emerging" can misinform. PPCPs have been recognized as environmental pollutants by various scientists and government agencies (such as the U.S. FDA) since the 1970s. The topic did not gain recognition by environmental scientists in general or by the public until the late 1990s. So in this sense, the issue is "emerging" as one of widespread discussion. Further discussion of "emerging" pollutants/risks can be found at:

http://www.epa.gov/nerlesd1/chemistry/pharma/science-issues.htm
http://www.epa.gov/nerlesd1/chemistry/pharma/images/book_jasma.pdf

- concluded -

“Environmental Surprise”

The concept of "surprise" in environmental systems perhaps originally formalized by the ecologist Crawford S. (Buzz) Holling in the early 1970s. "Surprise" occurs when:

“... causes turn out to be sharply different than was conceived, when behaviors are profoundly unexpected, and when action produces a result opposite to that intended - in short, when perceived reality departs qualitatively from expectation.”

Holling, C.S. 1986. “The resilience of terrestrial ecosystems: local surprise and global change.” In: Sustainable Development of the Biosphere, Clark, W.C. & R.E. Munn (Eds.), Cambridge University Press, Cambridge, UK, Chapter 10, 292-317.

continued -

“Environmental Surprise”

Surprise is “a condition in which perceived reality departs qualitatively from expectations”.

In Holling’s view, resilience may enable an ecosystem to return to a steady state after being subjected to an unusual event (or an ongoing succession of cumulative events) denoted as being a "surprise", but **the state to which it reverts may be different** – a discontinuous change.

- concluded -

PPCPs as Environmental Pollutants

- PPCPs are a diverse group of chemicals comprising all human and veterinary drugs (available by prescription or over-the-counter; including the new genre of "biologics"), diagnostic agents (e.g., X-ray contrast media), "nutraceuticals" (bioactive food supplements such as huperzine A), and other consumer chemicals, such as fragrances (e.g., musks) and sun-screen agents (e.g., methylbenzylidene camphor); also included are "excipients" (so-called "inert" ingredients used in PPCP manufacturing and formulation).
- Drugs differ from agrochemicals in that they often have multiple functional groups (many are amphiphilic) and usually have lower effective doses. This complicates fate/transport modeling and lends an extra dimension to the analytical techniques required for monitoring. Also designed for use by/for the individual.
- In contrast to the conventional PBTs, most PPCPs are neither bioaccumulative nor volatile; some, such as the musks, however, do indeed fulfill the criteria for PBTs.

Excipients

Traditionally but inaccurately referred to as “inert ingredients”. But actually serve sometimes as “co-therapeutics”, adding certain functionality to the active ingredient (e.g., enhancing delivery and improving dosage/absorption) or permitting proper production/formulation (e.g., fillers, lubricants).

While classified as GRAS, excipients can cause side effects (one proposal possibly explaining a performance difference between generics and brand names)

IPEC – *International Pharmaceutical Excipients Council* (trade organization): www.ipec.org

Manufacturing rate: hundreds of thousands of tons per year.

continued -

Excipient Classes Include:

- **Binders**: starch, celluosics
- **Disintegrants**: microcrystalline cellulose
- **Fillers** (diluent enhancers), Compression Aids, Suspending/Dispersants: lactose, calcium phosphate
- **Lubricants** (mold releasers): stearates
- **Glidants** (flow enhancers): silicon dioxide
- **Colorants**: azo, triphenylmethane, quinoline, xanthine dyes
- **Sweeteners**: synthetic (aspartame, saccharin) and natural (fructose)
- **Preservatives** (antimicrobials): chlorobutanol, phenol, benzoates
- **Film/Coatings**: shellac
- **Flavors**: proprietary “trade secrets”
- **Printing inks** (identification)

- concluded -

Inter-Connectedness of Humans and the Environment

- Occurrence of PPCPs in the environment mirrors the intimate, inseparable, and immediate connection between the actions and activities of individuals and their environment.

- PPCPs owe their origins in the environment to their worldwide, universal, frequent, and highly dispersed but cumulative usage by multitudes of individuals.

Origins of PPCPs in the Environment

- Portions of most ingested drugs are excreted in varying unmetabolized amounts (and undissolved states, primarily because of protection by excipients) primarily via the urine and feces.

- Other portions sometimes yield metabolites that are still bioactive. Still other portions are excreted as conjugates.

- Free excreted drugs and derivatives can escape degradation in municipal sewage treatment facilities (removal efficiency is a function of the drug's structure and treatment technology employed); the conjugates can be hydrolyzed back to the free parent drug.

- Un-degraded molecules are then discharged to receiving surface waters or find their way to ground waters, e.g., leaching, recharge.

continued -

Overview: Pharmaceuticals in the Environment

- Certain pharmaceutically active compounds (e.g., caffeine, aspirin, nicotine) have been known for over 20 years to occur in the environment.
- Environmental occurrence primarily resulting from treated and untreated sewage effluent.
- Only more recently has a larger picture emerged — numerous PPCPs can occur (albeit at very low concentrations).
- Prior discovery delayed primarily by limitations in analytical environmental chemistry (ultra-trace enrichment and detection).
- Domestic sewage is a major source — not just hospital sewage. CAFOs are a major source of antibiotics and possibly steroids.

continued -

Overview: Pharmaceuticals in the Environment

- Continual input of PPCPs to aquatic environment via sewage can impart a persistent quality to those compounds that otherwise possess no inherent environmental stability.

- The full extent, magnitude, and ramifications of their presence in the aquatic environment are largely unknown.

- Vast majority of all ecological monitoring studies to date have been performed in Europe.

- Use/release of **antibiotics** and natural/synthetic **steroids** to the environment has generated most of the controversy to date, **but a plethora of other PPCPs have yet to be examined**. Scope of overall issue is ill-defined.

continued -

Overview: Pharmaceuticals in the Environment

- Toxicological significance for both humans and ecological exposure to multiple chemicals at trace concentrations (ppb-ppt) for long durations is poorly understood.

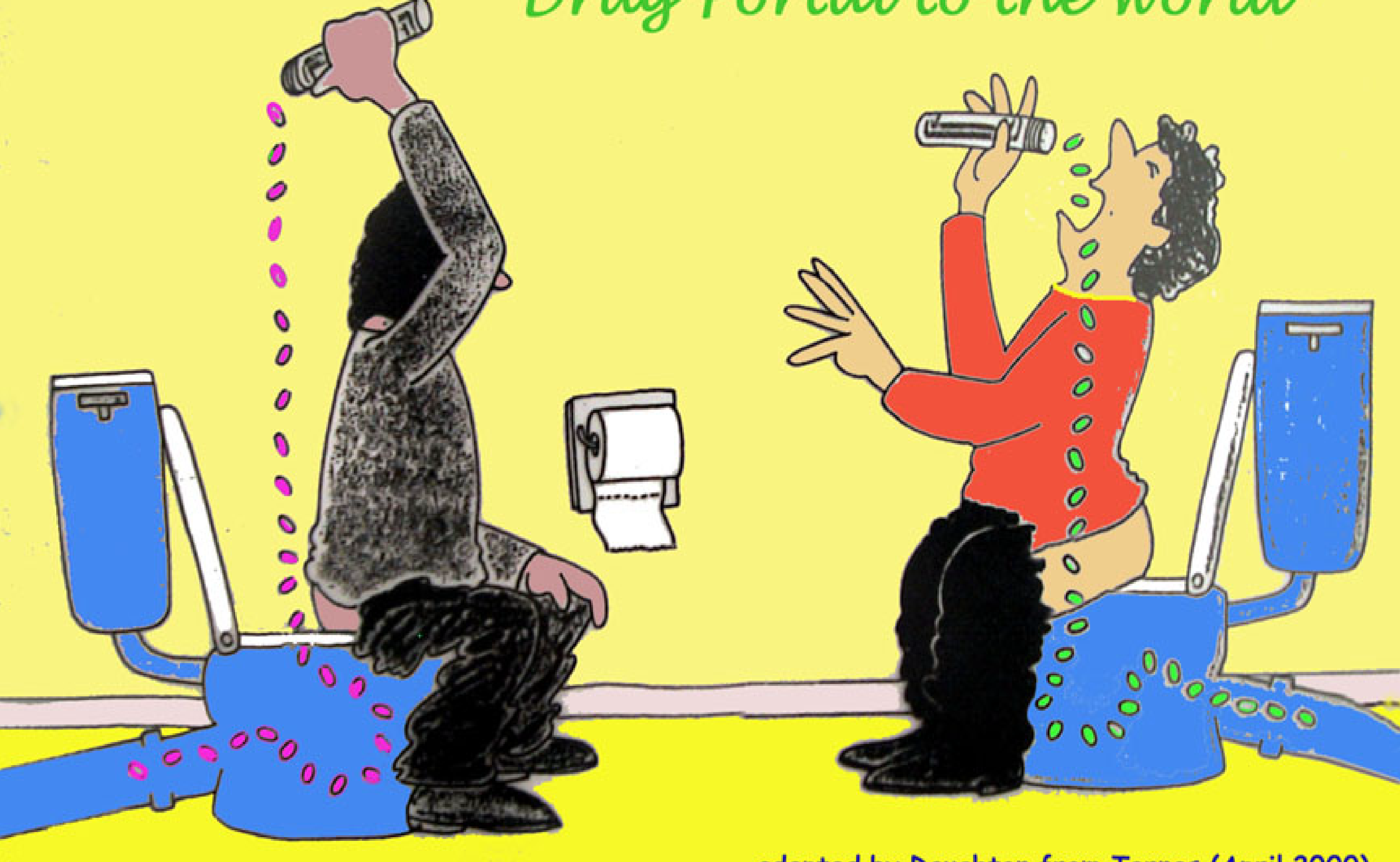
- If PPCPs eventually prove to be an environmental concern, it is unknown whether sewage treatment facilities could be cost-effectively modified to reduce emissions.

- Source control (aimed at both disposal and medical practices) may prove more effective.

- Focus should be on proper and sufficient science for establishing occurrence, exposure, susceptibility/effects, so that sound decisions can be made regarding human and ecological health.

- concluded -

Drug Portal to the World

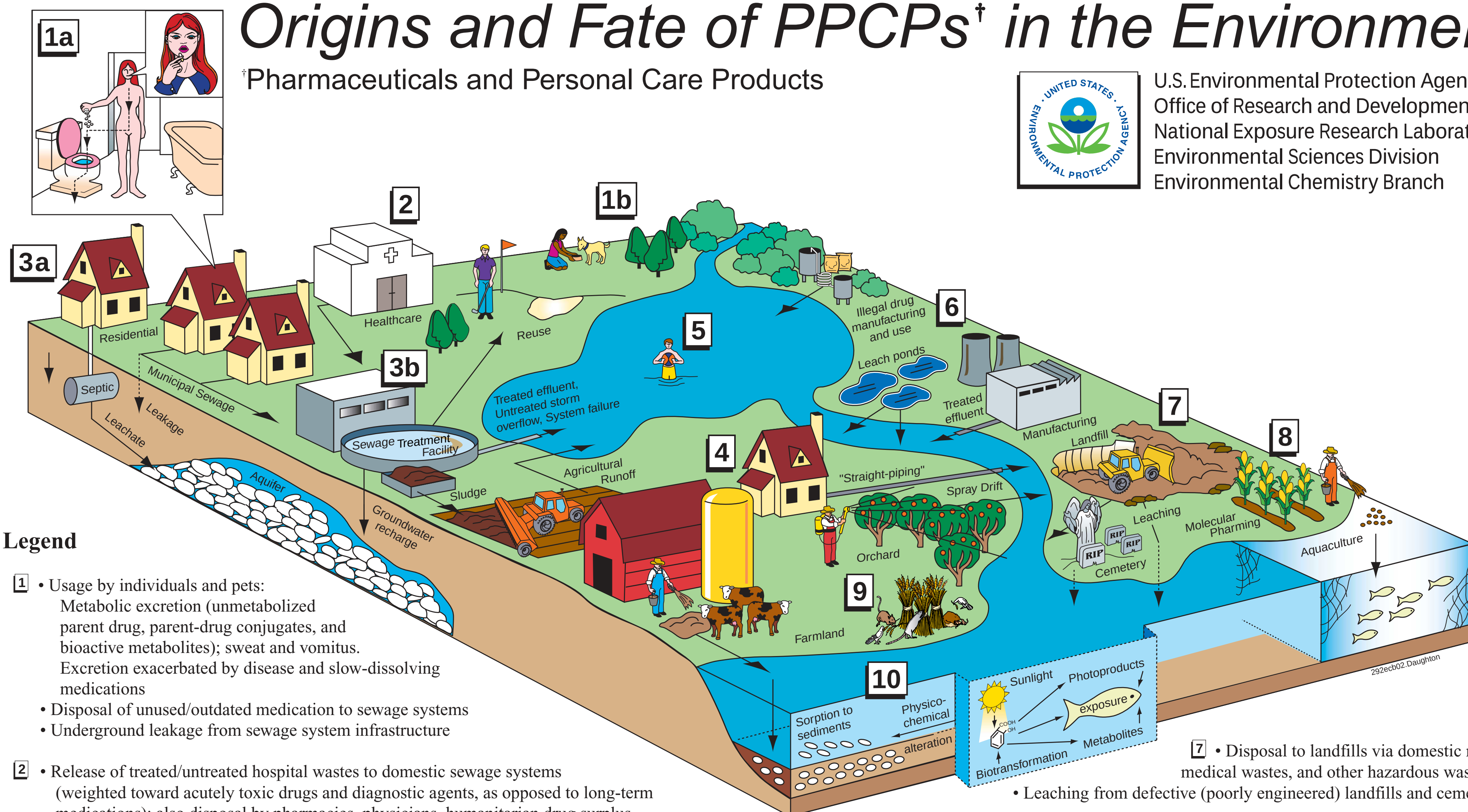


adapted by Daughton from Ternes (April 2000)

Origins and Fate of PPCPs† in the Environment

†Pharmaceuticals and Personal Care Products

U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory
Environmental Sciences Division
Environmental Chemistry Branch



Legend

1 • Usage by individuals and pets:
Metabolic excretion (unmetabolized parent drug, parent-drug conjugates, and bioactive metabolites); sweat and vomitus. Excretion exacerbated by disease and slow-dissolving medications
• Disposal of unused/outdated medication to sewage systems
• Underground leakage from sewage system infrastructure

2 • Release of treated/untreated hospital wastes to domestic sewage systems (weighted toward acutely toxic drugs and diagnostic agents, as opposed to long-term medications); also disposal by pharmacies, physicians, humanitarian drug surplus

3 • Release to private septic/leach fields
• Treated effluent from domestic sewage treatment plants discharged to surface waters or re-injected into aquifers (recharge)
• Overflow of untreated sewage from storm events and system failures directly to surface waters

4 • Transfer of sewage solids ("biosolids") to land (e.g., soil amendment/fertilization)
• "Straight-piping" from homes (untreated sewage discharged directly to surface waters)
• Release from agriculture: spray drift from tree crops (e.g., antibiotics)
• Dung from medicated domestic animals (e.g., feed) - CAFOs (confined animal feeding operations)

5 • Direct release to open waters via washing/bathing/swimming

6 • Discharge of regulated/controlled industrial manufacturing waste streams
• Disposal/release from clandestine drug labs and illicit drug usage

7 • Disposal to landfills via domestic refuse, medical wastes, and other hazardous wastes
• Leaching from defective (poorly engineered) landfills and cemeteries

8 • Release to open waters from aquaculture (medicated feed and resulting excreta)
• Future potential for release from molecular pharming (production of therapeutics in crops)

9 • Release of drugs that serve double duty as pest control agents:
examples: 4-aminopyridine, experimental multiple sclerosis drug → used as avicide; warfarin, anticoagulant → rat poison; azacholesterol, antilipidemics → avian/rodent reproductive inhibitors; certain antibiotics → used for orchard pathogens; acetaminophen, analgesic → brown tree snake control; caffeine, stimulant → *coqui* frog control

10 Ultimate environmental fate:
• most PPCPs eventually transported from terrestrial domain to aqueous domain
• phototransformation (both direct and indirect reactions via UV light)
• physicochemical alteration, degradation, and ultimate mineralization
• volatilization (mainly certain anesthetics, fragrances)

Sources of Raw Sewage in U.S.

released to streams, lakes, estuaries, oceans, groundwater

- **combined sewer overflows** (CSOs) = **4.5 X 10^{12} L/year**
- [CSOs handle rainwater runoff, domestic sewage, and industrial wastewater, and are designed to discharge untreated sewage during adverse storm events] †

† http://cfpub.epa.gov/npdes/home.cfm?program_id=5

- **sanitary sewer overflows** (SSOs) [severe weather, system malfunction, improper system operation/maintenance]
- **leakage** from sewage transport infrastructure [sewer pipe cracks caused by tree roots and defective/collapsed pipes]
- failing **septic systems** [1990 U.S. census showed ca 25% of all housing units use on-site wastewater handling system (e.g., septic system); see "SepticStats: An Overview", Graham Knowles, 1998: http://www.nesc.wvu.edu/images/SepticStat.pdf. In certain, the percentage is much higher.
- unpermitted **privies**
- **straight-piping**

continued -

Sources of Raw Sewage in U.S.
- Contamination of Beaches -

NRDC Report: ***Testing the Waters 2002 - Guide to Water Quality at Vacation Beaches*****, August 2002.**

http://www.nrdc.org/water/oceans/ttw/titinx.asp

See Chapter 1: ***Sources of Beachwater Pollution***

http://www.nrdc.org/water/oceans/ttw/chap1.asp#table3

Sources of Raw Sewage in U.S.

contributions from **septic systems,** unpermitted **privies**, **and straight-piping are unknown**

Drinking & Waste Water Infrastructure Needs

2001 Report Card for America's Infrastructure

American Society of Civil Engineers (ASCE)

(http://www.asce.org/reportcard/index.cfm?reaction=full)

Nationwide grades of “D” assigned for both drinking water and wastewater infrastructures
(http://www.asce.org/reportcard/index.cfm?reaction=full&page=2)

Over $20 billion dollars annually is the estimated need for rectifying the nation’s degenerating water/waste infrastructures:

“The nation's 54,000 drinking water systems face an annual shortfall of $11 billion needed to replace facilities that are nearing the end of their useful life and to comply with federal water regulations. Non-point source pollution remains the most significant threat to water quality.”

“The nation's 16,000 wastewater systems face enormous needs. Some sewer systems are 100 years old. Currently, there is a $12 billion annual shortfall in funding for infrastructure needs in this category; however, federal funding has remained flat for a decade. More than one-third of U.S. surface waters do not meet water quality standards.”

Nationwide studies relevant to potential for PPCP occurrence and distribution in the environment

- 1999-2000: USGS implemented **first-ever U.S. national reconnaissance of "emerging pollutants" in waters**
  - objective was to establish baseline occurrence data
  - included were some commonly used PPCPs
  - data collected from 142 streams, 55 wells, 7 effluents (in 36 states)
  - findings published in 15 March 2002 issue of:
    Environmental Science and Technology
  - detailed information available at:
    http://toxics.usgs.gov/highlights/whatsin.html

- 2001: **first-ever study published on geographic variation** (across U.S.) **of prescription drug usage**:
  Prescription Drug Atlas (Express Scripts, 2001), available at:
  http://www.express-scripts.com/other/news_views/outcomes_research/atlas2002/atlas_ex_sum.htm

Environmental Disposition of PPCPs in Sewage Biosolids

A July 2002 report issued by the NRC reassesses the unknowns regarding the environmental disposition of sewage biosolids:

- "*Biosolids Applied to Land: Advancing Standards and Practices*," Committee on Toxicants and Pathogens in Biosolids Applied to Land, National Research Council, ca. 220 pp, 2002 (available at: http://www.nap.edu/books/0309084865/html/)

continued -

Environmental Disposition of PPCPs in Sewage Biosolids

Highlights of the report that are directly relevant to PPCPs include:

- (i) Pharmaceuticals and synthetic musks are mentioned repeatedly in Chapter 5: "Evaluation of EPA's Approach to Setting Chemical Standards"

- (ii) The NRC Committee recommends that a new national survey be considered of chemicals in sewage sludge. PPCPs were highlighted as one class that was not considered in EPA's prior 1993 survey [more information regarding biosolids in general can be found at: http://www.epa.gov/epaoswer/non-hw/compost/biosolid.pdf].

- (iii) The NRC recommends that another chemical selection process be conducted to determine which additional chemicals should be considered for regulation.

- (iv) In reconsidering the Part 503 Biosolids Rule (http://www.epa.gov/OW-OWM.html/mtb/biosolids/503pe/index.htm), the NRC recommends that the EPA should consider toxic end points (and chemical interactions) that were not considered in the original assessment.

continued -

Environmental Disposition of PPCPs in Sewage Biosolids

- (v) Page 183 states: "Two categories of chemicals deserving special attention are pharmaceuticals and odorants" (also included are the synthetic musks). "Considering the amounts discharged to sewage systems, the presence of pharmaceuticals in biosolids has not been adequately investigated."

- (vi) The NRC recommends: "...that a research program be developed for pharmaceuticals and other chemicals likely to be present in biosolids that are not currently included in routine monitoring programs."

- (vii) The issues associated with antibiotics (resistance selection and transfer) are covered in Chapter 6.

- concluded -

Origins of PPCPs in the Environment

- Other potential routes to the environment include leaching from municipal landfills, runoff from confined animal feeding operations (CAFOs) and medicated pet excreta, loss from aquaculture, spray-drift from agriculture, direct discharge of raw sewage (storm overflow events & residential "straight piping"), sewage discharge from cruise ships (millions of passengers per year); in the future, the possibility exists for the future transgenic production of proteinaceous therapeutics by genetically altered plants (aka "molecular farming" — "biopharming") [see: http://www.epa.gov/nerlesd1/chemistry/ppcp/relevant.htm#Molecular Farming]

- Direct discharge to the environment also occurs via dislodgement/washing of externally applied PPCPs.

continued -

Drugs Having Double Uses: Medicinals and Pest-Control Agents (alternative sources for introduction to the environment)

Some chemicals serve double duty as both existing/experimental drugs and as pest-control agents. While this shows the broad utility of certain drugs, it also poses the possibility that these alternative uses serve as additional sources for their introduction to the environment. The potential significance of these alternative uses as sources for environmental release has never been explored. *Examples include:*

- **4-aminopyridine**: experimental multiple sclerosis drug and an **avicide**
- **warfarin**: anticoagulant and a **rat poison**
- **triclosan**: general biocide and **gingivitis agent** used in toothpaste
- **azacholesterols**: antilipidemic drugs and **avian/rodent reproductive inhibitors** [e.g., Ornitrol]
- certain **antibiotics**: used for **orchard pathogens**
- **acetaminophen**: an analgesic and useful for control of **brown tree snakes**
- **caffeine:** stimulant and approved for control of ***coqui* frog** in Hawaii; also repels and kills snails and slugs at concentrations exceeding 0.5%.

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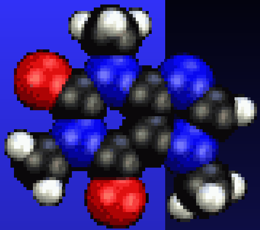


Caffeine for control of frog pests

U.S. EPA approved (27 Sept 2001) specific exemption from FIFRA allowing use of caffeine to control *coqui* frogs in Hawaii.

Exemption allows application of 100-200 pounds per acre (max total 1,200 lbs/year).

In absence of natural predators, *coqui* frog can reproduce to high densities (10,000/acre).

Out-compete native birds by massive consumption of insects.

Chirping frequency is extremely piecing and annoying (upwards of 100 db).

single chorus

Pharmaceuticals and Personal Care Products (PPCPs)

Fact: Certain PPCPs occur in the environment (esp. the aquatic environment)

Origins: Domestic sewage, hospitals, CAFOs

Issue: Fate and effects are poorly understood

Numerous questions…

Questions Deserving Attention?

- “Conventional”, regulated lists of “priority pollutants” (e.g., POPs) — Are POPs the only chemicals that deserve our attention regarding environmental fate and effects?

- PPCPs in aquatic environments receiving treated & untreated sewage (overflows/spills & “straight-piping”) — What is the spectrum of PPCP occurrence and prevalence?

- PPCPs leaching into groundwater from solid waste disposal or sewage sludge application — Is there any significance to PPCPs in groundwater? Are they persistent?

- PPCPs in treated wastewater intended for groundwater recharge — Is there cause for concern from recycled water?

continued -

Questions Deserving Attention?

- Low concentrations of PPCPs in the environment (especially in the aquatic realm) — Is there cause for concern regarding impact to non-target organisms?

- Potential effects of PPCPs on non-target species, many of which do not possess the same suite of receptors as humans — Do we know enough about receptor differences and similarities among target and non-target organisms?

- Individual PPCPs at low concentrations — Can multiple PPCPs sharing the same mode of action combine to reach threshold-effects levels?

continued -

Questions Deserving Attention?

- PPCPs that are continually introduced to aquatic environment — Is this a special exposure case since biota are exposed continually, through multiple generations?

- Cellular mechanisms in aquatic biota that confer protection from continual exposure (e.g., efflux pumps) — Can these protective cellular transport systems be inhibited by certain PPCPs, thereby compromising aquatic health?

- Acute toxicity, carcinogenesis, and mammalian endocrine disruption are highly visible concerns for many environmental pollutants — Should more attention be paid to other, less overt toxicological endpoints, such as immuno-disruption, neurobehavioral change, and other subtle effects?

continued -

Questions Deserving Attention?

- Practices partly contributing to introduction of PPCPs to the environment include direct disposal of excess/expired PPCPs to domestic sewage and landfills, and over-prescribing of various drugs — Should these practices be discouraged?
- Low levels of PPCPs in drinking water and shell/fin-fish — Can consumption by humans lead to significant exposures?
- In short: Is there the potential for unanticipated consequences of PPCPs in the environment? If so, where's the evidence? Do sufficient data exist to decide whether certain classes of PPCPs in the environment warrant a careful look, or can we ignore other classes?

- concluded -

Major Tasks for Science Community

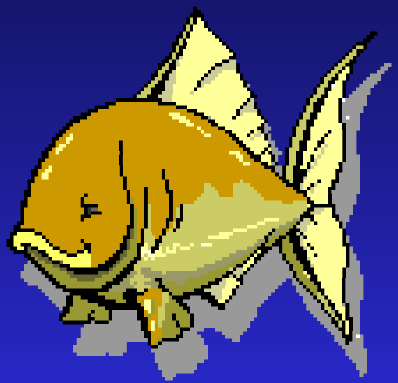
- Determine which therapeutic or consumer-use classes of PPCPs have an environmental presence and what their trends are.

- For each PPCP class known to be present in the environment at significant individual or combined concentrations, rule-in or rule-out possible deleterious environmental effects.

- Task will involve simultaneous work from both exposure and effects scientists working in parallel and in sequence.

Aquatic organisms — captive to continual, life-cycle chemical exposures

➢ Aquatic Exposure is Key: Any chemical introduced via sewage to the aquatic realm can lead to continual, multigenerational exposure for aquatic organisms.



Re-evaluation of "Persistence": Chemicals continually infused to the aquatic environment essentially become "persistent" pollutants even if their half-lives are short — their supply is continually replenished (analogous to a bacterial chemostat). These can be referred to as ***pseudo-persistent*** **chemicals** (**P2's**).

Subtle (currently unrecognized) Effects: a Troubling Scenario?

- Uses for which PPCPs were designed differ radically from those of industrial and agro-chemicals.

- Intended biological targets (receptors) are numerous and frequently exquisitely specific and sensitive.

- Intended/unintended receptors of exposure and effects can differ greatly from those of currently regulated pollutants.

- Receptors in non-target species could differ from those in humans.

continued -

Subtle (currently unrecognized) Effects:

some examples:

- Profound effects on development, spawning, and wide array of other behaviors in shellfish, ciliates, and other aquatic organisms by SSRI and tricyclic antidepressants.
- Dramatic inhibition of sperm activity in certain aquatic organisms by calcium-channel blockers.
- Antiepileptic drugs (e.g., phenytoin, valproate, carbamazepine) have potential as human neuroteratogens, triggering extensive apoptosis in the developing brain → neurodegeneration.
- ppm and sub-ppm levels of various drugs (NSAIDS, glucocorticoids, anti-fibrotics) affect collagen metabolism in teleost fish, leading to defective/blocked fin regeneration
- Multi-drug transporters (efflux pumps) are common defensive strategies for aquatic biota — possible significance of efflux pump inhibitors in compromising aquatic health?

continued -

Subtle Effects: Multi-Drug Transporters

- General "Chemical Defense System" in aquatic biota.

- Multi-drug transporters — a.k.a. efflux pumps — confer "multi-drug resistance" (MDR) or multi-xenobiotic resistance (MXR).

- Membrane-based active transport systems that "eject" or "pump" toxicants from inside cells (best characterized are the "P-glycoprotein-like" – Pgp – transporter systems).

- Prevent intracellular accumulation of toxicants and bioactive metabolites — allow cellular functioning in presence of extracellular toxicant concentrations that would otherwise prove toxic. Broad substrate specificity.

continued -

Subtle Effects: Multi-Drug Transporters

- Any of a diverse array of certain chemicals can inhibit these pumping systems, thereby potentiating adverse effects from extracellular toxicant concentrations that otherwise prove benign.

- Efflux Pump Inhibitors: a.k.a. "efflux pump reversal agents", "chemosensitizers", "efflux pump blockers", or "efflux pump inhibitors" (EPIs) [some of more potent being verapamil, reserpine, cyclosporin].

- Now recognized for enabling significant portion of increasing incidence of antimicrobial resistance among bacteria, these systems may also play critical role in protecting cells from toxicants (e.g., esp. in aquatic realm where filter-feeding organisms suffer continual, maximal exposure to toxicants).

continued -

Subtle Effects: Multi-Drug Transporters

- When aquatic MXR is expressed, intracellular concentration of toxicants will not accurately reflect actual exposure concentrations. When body-burdens of pollutants in aquatic organisms are used as indicators for exposure concentrations, the lower-than-expected bioaccumulated loads will bias these extrapolations low.

- Does the continual need to express and maintain high-levels of MXR impose a burdensome energy cost on aquatic organisms, thereby jeopardizing overall health or survival advantage?

- Would organisms in less-polluted aquatic environments be at higher risk to newly introduced toxicants because of their lower induced levels of MXR?

- Can broad-spectrum antiseptics such as triclosan promote wide-spread antibiotic resistance simply by inducing efflux pumps?

continued -

Subtle Effects: Multi-Drug Transporters

- Those chemicals that induce expression of efflux pump systems add another dimension to potential impacts by selectively enriching populations for resistant individuals (of seemingly good health) but paradoxically placing the entire population at maximum risk should they eventually be exposed to potent EPIs.

- Can systems in apparent good health possibly collapse simply by exposure to one or a series of EPIs (which by themselves would not prove toxic), simply from potentiating the action of toxicants that were already present?

- Summary of MXR: Cellular expression of these transport systems serves simultaneously as a marker of exposure, as a marker of effects, and as an indication of overall "health" (i.e., the ability to survive adverse chemical exposures).

continued -

Subtle (currently unrecognized) Effects: a Troubling Scenario?

- Could immediate biological actions on non-target species be imperceptible but nonetheless lead to adverse impacts as a result of continual accretion over long periods of time? For example, latent damage, only surfacing later in life. The issue of "resiliency".

- Could subtle effects accumulate so slowly (perhaps seeming to be part of natural variation) that major outward change cannot be ascribed to the original cause?

- Effects that are sufficiently subtle that they are undetectable or unnoticed present a challenge to risk assessment (especially ecological) — e.g., subtle shifts in behavior or intelligence.

- Advances required in developing/implementing new aquatic toxicity tests to better ensure that such effects can be detected.

- concluded -

Sidebar: Incremental Poisoning Designed to Appear "Natural" – a "Popular" Historical Practice

The use of slow poisoning in homicides (usually administered by food and drink) was practiced widely in Europe from the early to late 1600s – with a resurgence in the 1800s:

"The atrocious system of poisoning, by poisons so slow in their operation, as to make the victim appear, to ordinary observers, as if dying from a gradual decay of nature, has been practised in all ages."

"Those who are curious in the matter may refer to Beckmann on Secret Poisons, in his History of Inventions, in which he has collected several instances of it from the Greek and Roman writers. Early in the sixteenth century the crime seems to have gradually increased, till, in the seventeenth, it spread over Europe like a pestilence. It was often exercised by pretended witches and sorcerers, and finally became a branch of education amongst all who laid any claim to magical and supernatural arts. In the twenty-first year of Henry VIII. an act was passed, rendering it high-treason: those found guilty of it, were to be boiled to death."

The Slow Poisoners in

Extraordinary Popular Delusions and the Madness of Crowds

by Charles MacKay, 1841

Sidebar: **Toxicity versus Therapeutic Effect**

Paracelsus (1493-1541)

Theophrastus Phillippus Aureolus Bombastus von Hohenheim born in Einsiedeln, Switzerland

"All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy."

"**The dose makes the poison**."

Embodied in the concept of "**therapeutic index**" or therapeutic window, range, or ratio (selectivity) — ratio of the drug dose producing an undesired effect to the dose causing the desired effects.

NOTE

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Continue with part 3…